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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 08/078,768 | 06/16/1993 | RICHARD H. TULLIS | PMB9658 | 9155 |

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John W. Caldwell
WOODCOCK WASHBURN KURTZ MACKIEWICZ & NORRIS LLP
One Liberty Place 46th floor
Philadelphia, PA 19103

| EXAMINER | |
|---|---|
| MARTINELL, JAMES | |
| **ART UNIT** | **PAPER NUMBER** |
| 1633 | 68 |

DATE MAILED: 12/17/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 08/078,768 | TULLIS, RICHARD H. | |
| | Examiner | Art Unit | |
| | James Martinell | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *23 April 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *64-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *64-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *67* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

This application has been remanded to the examiner from the Board of Patent Appeals and Interferences (paper no. 64, mailed February 28, 2001). The Board of Patent Appeals and Interferences urged the examiner to take whatever action he should deem appropriate. Appellant has submitted documents from proceedings at the European Patent Office in connection with the decision revoking European Patent, EP 0 092 574, which corresponds to the instant application. While similar, the claims in EP 0 092 574 are not identical to the claims in the instant application. Prosecution on the merits is re-opened. This Office action clarifies the issuance of U.S. Patent No. 5,919,619 and the rejection of claims 64-72 of the instant application under 35 U.S.C. § 112, first paragraph. This Office action also takes into the account the documents of record in connection with the decision revoking the European Patent (EP 0 092 574) insofar as those documents are relevant to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 71 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,023,243. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1 of U.S. Patent No. 5,023,243 is a specific embodiment of the generic method of claim 71 in the instant application.

Claims 64-72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited to the preparation of stabilized forms of oligodeoxyribonucleotides that are phophotriesters, does not reasonably provide enablement for all stabilized forms of

oligodeoxyribonucleotides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The instant application does not give one of skill in the art guidance in connection with other forms of oligodeoxyribonucleotides that would be stable in vivo (see the Office action mailed April 1, 1992, page 2 and the Examiner's Answer, page 5). In the absence of such a teaching, it would require undue experimentation for one of skill in the art to discover and synthesize such compounds. Gura summarizes the problems encountered by those in the "antisense" field over the past several years. Rojanasakul discusses the problems associated with antisense therapy in more detail than Gura. Among the problems discussed in Rojanasakul are stability, specificity, and cellular uptake (e.g., see the abstract and pages 118-120). Antisense technology involves the use of usually short nucleotides (usually single stranded DNAs or single stranded DNAs with modified backbones) to inhibit the expression of gene is cells in vivo or in vitro by the mechanism of nucleic acid molecular hybridization inside the cell or by triple helix formation. The instant application concerns an antisense method of specific inhibition of protein synthesis by the nucleic acid molecular hybridization of an oligonucleotide to the coding region of mRNA inside of a cell, the cell being in an organism, or an in vitro environment outside of an organism. Gura indicates that a number of problems exist in actually getting these types of methods to work. The Office action mailed April 1, 1992 mentioned that one of these difficulties is the stability of the oligonucleotides in vivo and further indicated that method claims that embraced in vivo use of oligonucleotides were broader that the enabling disclosure. A later Office action (mailed February 22, 1994) pointed out that references cited by appellant do not address questions of the ability of oligonucleotides to enter cell, the ability of oligonucleotides to enter cells, the ability of oligonucleotides to specifically hybridize to the target, or in vivo stability. Thus, there are two issues at hand. First, the instant application does not teach one of skill in the art the full scope of the claimed invention in the sense that the application adequately identifies stabilized oligonucleotides other than those that are phosphotriesters. Applicant has been granted a patent (U.S. Patent No. 5,023,243) limited to antisense methods of using phosphotriesters. Second, the instant application does not provide an enabling

disclosure for the use of deoxyribonucleotides in vivo. Applicant has been granted a patent (U.S. Patent No. 5,919,619) limited to the methods of inhibiting expression using stabilized oligonucleotides on cells in culture. Thus, the instant claims (except for claim 71 which is limited to stabilized oligonucleotides) differ in two (not one) limitations from the claims of the '619 patent. The prosecution history of the '619 patent shows that the application enables the practice of inhibition of expression only in cells in culture and only using stabilized oligonucleotides. The following is from the Examiner's Reasons for Allowance in the '619 patent:

> The following is an examiner's statement of reasons for allowance.
> Claims 53-65 are allowable in view of the arguments and remarks made by Appellant in the Brief in connection with the Zamecnik et al reference (Zamecnik et al, Proc. Natl. Acad. Sci. USA 75: 280-284 (1978)). See the Brief filed September 17, 1998, pages 17, 20-22, and 25. Zamecnik et al discloses that oligonucleotides are capable of entering cells in culture. The reference further indicates the probable mode of action of certain oligonucleotides to be hybridization with viral sequences within the cells.

The limitation of the method for use in cell only in culture is important to the consideration of claims in the '619 patent because the issue of breakdown of the oligonucleotides in body tissues was not a factor in a cell culture environment. (Sometimes biochemical or molecular biological processes within cells in culture are referred to in the art as being in vitro in the art even though the cells in culture are alive, at other times in the art biochemical or molecular biological processes within cells in culture may be referred to as being in vivo because the cells are alive, the terminology can lead to confusion, so it is wise to consider the larger context in which these terms are used.)

The Zamecnik et al reference discloses use of an unprotected oligonucleotide which would be expected to break down in vivo (see below) as applicant himself asserted in the parent file (see patented file U.S. Patent No. 5,023,243, paper no. 8, filed February 9, 1984, page 3), stating, "Zamecnik and Stephenson used an unprotected oligonucleotide, which would break down *in vivo* before having the desired effect."

Applicant's arguments (paper no. 15, pages 3-4) and Exhibits A-E submitted with the response filed October 1, 1992, and pages 6-21 of the brief are not convincing. First,

Exhibits A, B, and C were published subsequent to the effective filing date of the instant application. Appellant's argument that these articles ought to be convincing because they show the level of skill in the art at the time the invention was made is not convincing because of the rapid rate of developments in the field of chemical synthesis of oligodeoxyribonucleotides in the early 1980s. Because of the rapid rate of development at that time, the level of skill in the art could change rapidly over a period of only a few months. Thus, the citation of articles published in 1982, 1983, and 1984 in order to establish a level of skill in the art of oligodeoxyribonucleotide synthesis in 1981 is not convincing. Second, applicant's arguments and Exhibits A-E are not sufficient to overcome this rejection because none of Exhibits A-E discusses what is crucial to the use of oligodeoxyribonucleotides in this invention. For example, none of the references discusses (a) the ability of the particular oligodeoxyribonucleotides of any of the references to get into cells, (b) the ability of the particular oligodeoxyribonucleotides of any of the references to hybridize effectively and specifically to a nucleic acid of interest (i.e. a target nucleic acid), or (c) the in vivo stability of any particular oligodeoxyribonucleotides of any of the references. Therefore, given the lack of guidance as to which types of oligodeoxyribonucleotides to use in the instant invention or even the mere mention of potential candidate oligodeoxyribonucleotides to use and the failure of applicant to establish that one of skill in the art would readily know which oligodeoxyribonucleotide to use in the absence of such a disclosure in the instant application, one of skill in the art would be compelled to undertake undue experimentation in order to practice the invention as claimed. Additionally, the instant application provides no data and provides no methods for actually getting short DNAs or RNAs into cells. Applicant's arguments (paper no. 28),

the declarations by Drs. Ruth and Schwartz (filed September 6, 1994), and pages 6-21 of the brief are not convincing because these arguments and declarations do not address the issue of stability of the oligodeoxyribonucleotides in vivo (the declarations are silent on this issue). Paper no. 28 at page 5, first full paragraph asserts that the use of a stabilized nucleic acid is not the inventive principle of the instant invention and that any nucleic acid will work in the claimed method. This argument is most unconvincing in view of the argument made by applicant in the parent application (see patented file of U.S. Patent No. 5,023,243, paper no. 8 (filed February 9, 1984), page 3) wherein applicant says of a reference, "Zamecnik and Stephenson used an unprotected oligonucleotide, which would break down in vivo before having the desired effect." Thus, appellant's assertion that any nucleic acid will work is in conflict with applicant's earlier statement.

Applicant's arguments (paper no. 33) and the declarations by Drs. Schwartz and Ruth (filed April 17, 1995) and the attachments are not convincing. The following is added in rebuttal to arguments advanced by applicant.

(a) Applicant's arguments under section A of paper no. 33 are not convincing. Applicant asserts that, "The Examiner has previously urged that at the time of filing of the parent application in October of 1981, there were no other stabilized oligonucleotides reported in the literature." This assertion is made without reference to where in the file such an "urging" appears. Reference to the Office action mailed December 16, 1992 reveals the actual issue, which is that the instant application fails to guide those of skill in the art as to which oligodeoxyribonucleotides to use. Hence, all of applicant's arguments

in connection with the existence of any particular form of oligodeoxyribonucleotide at any time prior to the filing of the instant application are most unconvincing in the absence of a mention or teaching in the application as to how to use them. In fact, the instant application fails to even mention the different forms of oligodeoxyribonucleotides in any specific manner.

(b) Applicant's arguments and remarks in section B of paper no. 33 are most unconvincing because applicant has misidentified the statutory basis of the rejection. Applicant acknowledges (page 8) that the examiner has previously explained to applicant that the statutory basis of the rejection is 35 U.S.C. § 112, first paragraph and does not include 35 U.S.C. § 101 (utility). Accordingly, appellant's arguments in connection with utility are superfluous at best, but are given no weight at all in connection with the rejection under 35 U.S.C. § 112, first paragraph. Appellant additionally argues (page 11) that several references support the notion that intact oligonucleotides can be delivered to animals and isolated cells. This argument is not convincing because each of the articles cited was published subsequent to the effective filing date of the instant application. In addition, the following are noted.

(1) Michelson et al (Exhibit 3) does not disclose the use of a single stranded oligonucleotide, but is concerned only with the stability of a double stranded RNA in vivo. Applicant fails

to argue, and the declarations fail to reveal, how an already double stranded molecule could have any function at all as an antisense molecule, nor do the argument or declarations say what relevance the stability of a double stranded molecule has to the stability of a single stranded molecule. Indeed, applicant simply submits the article, discloses the fact that the article was submitted, and makes no connection between the instant application, claims, or rejection and the article.

(2) Wolff et al (Exhibit 4) is not convincing. First, applicant incorrectly attributes disclosures in Wolff et al to Michelson et al (paper no. 33, page 11 and pages 6 of each of the declarations by Drs. Ruth and Schwartz). Second, the reference says nothing at all about single stranded oligonucleotides.

(3) Lin et al (Exhibit 5) and the arguments in connection with it are not convincing because the reference does not deal with single stranded oligonucleotides.

(4) Wolff et al (Exhibit 6) and the arguments in connection with it are not convincing because the reference does not deal with single stranded oligonucleotides.

(5) Each of Phillips et al (Exhibit 7), Akabayashi et al (Exhibit 8), and Hijya et al (Exhibit 9) teaches the use of oligodeoxyribonucleotides in vivo. Applicant's reliance on

these references to complete the application is insufficient because each of these references was published in 1994, which is after the effective filing date of the instant application.

(c) Applicant argues (paper no. 33, section C) that the examiner misinterpreted a statement made by the inventor during the prosecution history of a prior application. Applicant's argument is unconvincing in the face of the simple, direct, and unambiguous language used by the inventor. Applicant's arguments are further unconvincing in view of published statements under the name of the inventor and others. For example, in the publication by Tullis et al (Biotechnology International, 1992, reference A15, already of record) state on page 79 that one of the key events in the development of antisense technology was the development was more efficient systems for the synthesis of normal and phosphorous modified oligodeoxyribonucleotides and then goes on to cite a number of references, all of which were published subsequent to the effective filing date of the instant application. (The Beaucage and Caruthers reference is listed as being published in 1980 at page 79, but is listed as published in 1984 in the bibliography. The 1984 date is almost certainly correct because the Beaucage and Caruthers reference is a European Patent application that was filed in 1982.) Additionally, at page 80 (top part of the right hand column), Tullis et al mention

problems with uptake and stability of unmodified oligonucleotides and give no clue to the reader to do any of the things that applicant now asserts would have been obvious to anyone of skill in the art in 1981. Thus, the evidence in the record indicates that applicant himself did not know that unmodified oligonucleotides could be used as antisense agents even as late as 1992.

(d) Applicant's argument in paper no. 33, section D is unconvincing. Applicant again incorrectly refers to a hybrid rejection under 35 U.S.C. §§ 101 and 112. Applicant then asserts that, "Once the inventive aspects of the oligonucleotides are recited, the practice of the invention is trivial . . . ." The argument fails to persuade because the premise is grounded in an incorrect assumption. The very issue here is whether the inventive aspect has been recited. In all the argumentation advanced by applicant, applicant fails to indicate where the application teaches or mentions the use of any specific modified oligonucleotides other than phosphotriesters or the use of unmodified oligonucleotides as antisense agents.

(e) Applicant's arguments (paper no. 33, section E) are unconvincing for reasons given in (a) - (d) above and reasons already of record.

Applicant filed a request for reconsideration on July 20, 1995 in connection with claim 71 only, which claim is directed to a method of inhibiting expression by using nuclease resistant oligonucleotides as antisense agents. Applicant continues to argue that those of skill in the art would know which oligonucleotides to use as antisense agents

given the instant disclosure. However, it cannot be agreed that the scant statements in the application (e.g., at page 4) in regard to the use of stabilized forms of oligonucleotides are in any way adequate direction for those of skill in the art as is required under the statute. Indeed, applicant's strenuous argumentation to the effect that those of skill in the art would be expected to do literature searches and would be led from the work of one researcher to another and would see that work on a background of hypothetical information that is only speculated at (e.g., see points 3, 4, and 5 on page 5 of the response filed July 20, 1995) all support the notion that the specification does not teach those of skill in the art how to make and use the invention. This is the standard of the statute and this is what is expected of the application. It is not enough to hint at what may be desirable, expecting those of skill in the art to perform the undue experimentation that is required to make the invention work. Finally, it is noted that point 6 on page 5 of the response filed July 20, 1995 is not an objective reason, but is an opinion; in fact, it is an opinion unsupported by objective evidence in the record.

## DISCUSSION OF THE BRIEF AND THE REPLY BRIEF

Appellant's arguments start at page 4. Pages 4-6 of the brief foreshadow the sections and arguments that appear later in the brief. The summary will not be discussed further here.

In section IV: 1 appellant asserts that one of skill would know that only a small class of well known nucleic acid analogs was being referred to in the specification. However, appellant does not point to anything in the application that points one of skill to any particular stabilized analogs of nucleic acids. Appellant frequently attempts to

paraphrase the examiner's position on this point, but does not meet the basis for the rejection directly. As stated in the first Office action on the merits, there is no guidance in the application to tell one of sill in the art which forms of oligodeoxyribonucleotides, other than phosphotriesters, would be stable in vivo. Appellant has given no evidence that it would not require undue experimentation to discover such compounds. In fact, the Gura and Rojanasakul references are evidence that undue experimentation would indeed have been necessary because this problem persists nearly 15 years after the effective filing date of the instant claims.

Appellant asserts that the examiner "cannot maintain this rejection because he was personally unaware that alternative analogs were known in the art." See brief, page 8, second full paragraph. This assertion of appellant is given no weight because the ignorance of the examiner was never used as a reason for the rejection.

Appellant's assert that any stabilized nucleic acid works (e.g., brief, paragraph bridging pages 8-9) is not convincing because it conflicts with each of Gura and Rojanasakul and because appellants have provided no evidence that any stabilized nucleic acid will work in the claimed methods. This argument is made in connection with appellant's assertion that claim 71 does not stand or fall with claims 64-70 and 72.

Section 1 B of the brief (pages 9-13) is not convincing for reasons given above in connection with the declarations of Drs. Schwartz and Ruth and in connection with the discussions of each of the references submitted as evidence in conjunction with those declarations.

Section 2 of the brief cannot be convincing. Appellant asserts that the "specification adequately teaches those of skill in the art which oligonucleotides to use and

how to use them to downregulate proteins (sic)." This lengthy argument cannot be convincing in the absence of even a mention of which oligonucleotides to use. The application is more a statement of a goal rather than a teaching of how to reach the goal.

Appellant asserts (section 3, pages 16-17 of the brief) that all stabilized oligonucleotides are taken up by cells. Each of Gura and Rojanasakul are at odds with this sweeping generalization. Hence, appellant's assertion is not convincing.

Section 4 of the brief (pages 18-20) contains another assertion by appellant that all stabilized nucleic acids will bind. Again, each of Gura and Rojanasakul disclose a different view (e.g., Gura at page 575, bottom half of column 1 and Rojanasakul at pages 119-120 (section 4.1)). It is noted that the claims require the specific inhibition of protein synthesis. Since each of Gura and Rojanasakul indicate that hybridization characteristics of stabilized forms of nucleic acids differ from those of non-modified forms and that non-specific effects are seen in cells treated with oligonucleotides, appellant's assertions and arguments cannot be persuasive.

Appellants also urge that the Gura and Rojanasakul references are irrelevant (Reply Brief, pages 9-13). Appellant argues that these references are irrelevant because they are concerned with clinical applications of antisense technology. This argument is not convincing because the references are not limited to clinical applications and because the references were cited to support the difficulties with antisense technology that have been at issue throughout the file history of the instant application. For example, the PTO position has long been that real problems exist in connection with stability of oligonucleotides, entry of oligonucleotides into cells, and targeting of stabilized forms of oligonucleotides (e.g., see the Office action mailed December 16, 1992, page 3). At page 11 of the Reply Brief, Appellant assets that the Rojanasakul reference supports Appellant's position in that Rojanasakul refers to work that apparently used increased concentrations of oligonucleotides to achieve the desired antisense effect

in a given system. Appellant the quotes from Rojanasakul. That this section of the reference supports Appellant's notion that the instant application enables one of skill in the art to practice the claimed invention cannot be concluded because Appellant points to no part of the application that would lead one of skill in the art to the same solution alluded to in Rojanasakul and because the realization that came "soon" according to the portion of Rojanasakul quoted by appellant actually came in 1990 (see reference [47] cited in Rojanasakul). This is a full nine years after the effective filing date of the instant application. Thus, Appellant argues that a realization that took eight or nine years in a very active field would have taken one of skill in the art only routine experimentation with the benefit of the instant application without saying what the instant application supplies that the rest of the art lacks. Thus, Appellant's argument is not convincing. Appellant further argues that Gura is not a peer reviewed article, but was written by a reporter. Appellant characterizes a simple question in the text as "silly hyperbole." This is not seen as either silly or hyperbole, but a valid question as to the mechanism of action of new drugs. One can infer little or nothing about the mechanism of action of a drug from the fact that clinical trials are underway. Appellant's derogatory remarks in connection with the source of the article are given no weight at all. Appellant has not offered any rebuttal to the substance of the Gura article. Finally, appellant asserts,

Appellant asserts that the rejection is "obviously a hybrid §§101/112 rejection" (brief, page 21, first full paragraph). This section of the brief (pages 20-23) is given no weight because, as has been emphasized throughout prosecution, there is no rejection in the application of any claim for lack of utility under 35 U.S.C. § 101.

Section 5 B of the brief (pages 23-26) discusses the six references submitted in connection with the declarations of Drs. Schwartz and Ruth. The brief (paragraph bridging pages 23-24 incorrectly states that exhibits 3-9 are six references, the references are numbered as exhibits 3-9 and so there are seven references. These references are discussed in detail above. Several of the references (Michelson et al (Exhibit 3), Wolff et al

(Exhibit 4), Lin et al (Exhibit 5), and Wolff et al (Exhibit 6)) do not deal with the use of single stranded oligonucleotides, so they cannot be used as evidence of the stability of single stranded oligonucleotides. Single stranded oligonucleotides are the only oligonucleotides that can be used in the claimed methods because double stranded oligonucleotides are not free to hybridize with mRNA. The remaining two references (Phillips et al (Exhibit 7), Akabayashi et al (Exhibit 8), and Hijya et al (Exhibit 9)) were each published in 1994, well after the effective filing date of the instant application. Appellant cannot rely on references filed after the effective filing date of the instant claims to complete the enablement requirement (*In re Glass*, 181 USPQ 31, CCPA 1974).

In section 5 C (pages 26-30 of the brief) appellant argues that statements made in the record of the parent application and again in print (Tullis et al, Biotechnology International (1992)) by appellant that unmodified oligonucleotides would not work in vivo because they would break down (see above) are not evidence of what was plainly stated in English. Appellant asserts that these statements are merely "poorly phrased" (see brief, page 26, the bold faced type). Again, on page 27 of the brief, appellant argues a utility rejection that is not in the application. This argument is not relevant because there is no rejection under 35 U.S.C. § 101 extant or extinct in the instant application. Additionally, appellant urges (last full paragraph on page 27 of the brief) that one of skill in the art need only just add more unmodified nucleic acid to make the method work. This argument is most unconvincing in view of appellant's own statements (in this entire record, the only statements by the inventor in connection with use of unmodified nucleic acids are the two alluded to above), the statements in each of Gura and Rojanasakul, and the absence of any teaching of "just adding more" in the instant application. The application is to be a guide

to those of skill in the art of how to practice the invention. Appellant has pointed to no guidance in the application as filed for "just adding more." Finally, appellant (brief, page 28, second full paragraph) claims that the sentence is poorly worded and can be interpreted differently. The sentence is, "Zamecnik and Stephenson used an unprotected oligonucleotide, which would break down in vivo before having the desired effect." To this the only reply can be A is A. Appellant urges that appellant should be able to retract misstatements. Fair enough. However, the inventor did not say this once, but at least twice and on one occasion in published work (and this more than a decade after the effective filing date of the instant claims). We have not heard from the inventor about this since and there is no evidence in the record that the inventor's own statements were incorrect. Much less do we have an indication in the application as filed that the inventor contemplated the "just add more" method. For these reasons, the simple, direct, plain, unambiguous, and clear wording of the statements are taken at face value.

Section 6 of the brief (pages 30-31) concerns itself with utility under 35 U.S.C. § 101 and will not be addressed in the absence of such a rejection in the record.

Section 7 of the brief (pages 31-34) is not convincing because it misstates the issue. Appellant asserts (paragraph bridging pages 31-32) that the type of nucleic acid used to bind the mRNA is irrelevant. This is incorrect. A casual review of this long record will reveal that that is precisely what is relevant. The relevance of this as an issue is embodied in the exposition of same in the rejection first made on April 1, 1992.

The following regards the documentation submitted in connection with the revocation of the European Patent:

(a) Several opposition papers were submitted to the EPO regarding the '574 European Patent. The examiner has considered these. The opposition papers in the aggregate refer to no fewer than 28 different references that are purported to make the claimed invention lack novelty or lack an inventive step. Some, but not all of the 28 references mentioned in the oppositions papers are of record in the instant application. Although the each of the opposition papers contains lengthy descriptions of prior art references, none of the opposition papers contains a cogent argument that connects the references together in such a manner, and containing statements of motivation such that one could conclude that one of ordinary skill in the art would have found the claimed invention obvious at the time of the invention. Accordingly, no prior art rejection appears in this Office action over any of the prior art of record. It is noted that the "Decision Revoking the European Patent" did not include lack of novelty or lack of inventive step as reasons for the decision (see Reasons for the Decision section, pages 5-11).

(b) The "Decision Revoking the European Patent" did include reasons for lack of sufficiency of disclosure. Although the reasons in this decision are not the same as outlined in the rejection hereinabove, there are allusions to uptake of oligonucleotides by mammalian cells.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James Martinell whose telephone number is (703) 308-0296. The fax phone number for Examiner Martinell's desktop workstation is (703) 746-5162. The examiner works a flexible schedule and can be reached by phone and voice mail. Alternatively, a request for a return telephone call may be e-mailed to james.martinell@uspto.gov. Since e-mail communications may not be secure, it is suggested that information in such requests be limited to name, phone number, and the best time to return the call.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah R. Clark, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

JAMES MARTINELL, Ph.D.
SENIOR LEVEL EXAMINER